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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/579,548 | 05/26/2000 | Alan H. Lazarus | 701826/50750 | 7491 |

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| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/579,548 | LAZARUS ET AL. | |
| | Examiner | Art Unit | |
| | Phillip Gambel | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,26,27 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *24, 26, 27, 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment, filed 11/14/03, has been entered.
Claims 27and 30 have been amended.
Claim 29 has been canceled. Claims 1-23, 25, 28 and 31-33 have been canceled previously.

Claims 24, 26, 27 and 30 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 11/14/03.
The rejections of record can be found in the previous Office Action, mailed 8/11/03.

3. Claims 24, 26, 27 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant's arguments, in conjunction with the Lazarus declaration under 37 C.F.R. § 1.132, filed 11/13/03, have been fully considered but are not found convincing.

Applicant argues in conjunction with the Lazarus declaration under 37 C.F.R. § 1.132 and submitted references that the presently used humanized in vivo animal model is an accepted model for the correlation of in vivo animal studies to in vivo results in patients with respect to testing in vivo effects of an immunotherapy or an inhibition of human alloimmunization, particularly with respect of a human antibody response.

While applicant has relied upon a model to test the inhibition of human alloimmune response with respect alloimmunization to platelet transfusions, the instant claims are broader than inhibiting alloimmunization in the context of platelet transfusion or possibly or with organ transplantation associated GVHD. The claims are broadly drawn to inhibiting any alloimmune response or anti-HLA alloimmune response, including certain diseases set forth in claim 30. These targeted endpoints and diseases are not limited to inhibiting alloimmunization of anti-HLA antibody responses, as suggested by applicant's model or applicant's co-authored reference Transfusion 39: 818-823, 1999 (e.g. see Introduction and Discussion).

The following of record is reiterated for applicant's convenience, as it addresses the administration of the 18KDa CD40L which was known in the art prior to the filing of this application to be a homotrimer (oligomer) in solution as set forth in Mazzei et al. (J. Biol. Chem. 270: 7025-7028,1995).

Given applicant's current claims limiting the claimed methods to the administration of soluble 18KDa recombinant human CD40L consisting of amino acids 108-261 set forth in SEQ ID NO: 1, which has been recognized as a CD40 agonist, the instant methods are subject to the enablement rejection set forth herein. As applicant notes, the 18KDa CD40L was known in the art prior to the filing of this application to be a homotrimer (oligomer) in solution, as set forth in Mazzei et al. (J. Biol. Chem. 270: 7025-7028,1995)
Therefore, the instant claims are limited to the soluble CD40L to a known oligomeric CD40L agonists and away from the referenced soluble monomeric CD40L antagonists.

It is acknowledged that the present invention shows that the 18KDa CD40L inhibits a secondary alloimmune response in an SCID experimental model engrafted with human lymphocytes which indicates that oligomeric 18 KDa CD40L is an antagonist rather than a CD40 agonist in a platelet HLA alloimmune immunization model.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting a secondary alloimmune response in an SCID experimental model engrafted with human lymphocytes would be predictive of treating the breadth of alloimmune responses, T cell responses, autoimmune diseases encompassed by the claimed methods.

There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit alloimmune responses, T cell responses, autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

As applicant acknowledges, the administration of soluble 18KDa recombinant human CD40L consisting of amino acids 108-261 set forth in SEQ ID NO: 1 has been recognized as a CD40 agonist.

Applicant has not addressed the following of record, which clearly indicates that the administration of soluble 18KDa recombinant human CD40L would act as an agonist and would have the effects opposite to that claimed (e.g. "inhibiting an alloimmune response") in a number if not most alloimmunization contexts or the diseases claimed (see claim 30), as broadly encompassed by the claimed methods.

For example, Aruffo et al. (U.S. Patent No. 6,376,459) discloses that treating subject associated with B cell activation comprise administering a ligand such as an antibody that binds CD40CR / CD40L and that CD40CR / CD40L was useful to promote B cell activation (see columns 15-18; Uses of Ligands That Bind to CD40CR and Uses of CD40CR). Here, the therapeutic endpoints and diseases targeted by employing CD40L antagonists and agonists are in direct contrast with the claimed use of soluble 18 KDa CD40L to inhibit cell mediated immune responses, including the use of soluble 18 KDa CD40L in treating or preventing diseases selected from the group set forth instant claim 30.

In addition, Aruffo et al. (U.S. Patent No. 5,540,926) (prior art of record) discloses that soluble gp39 may be used to increase an immune response as a type of adjuvant, while immunosuppression by my accomplished by modifying or linking gp39 with a cytotoxic drug (e.g. see columns 10-11, Utility of the Invention).

Further, Armitage (U.S. Patent No. 6,264,951) (prior art of record) discloses that oligomeric CD40L as agonists, while monomeric CD40L acts as antagonists (e.g. see column 10, paragraphs 2-3). Here, monomeric CD40L antagonists are useful for treating autoimmune diseases encompassed by the claimed methods.

As indicated previously, it is noted that Lazarus et al. (Transfusion 39: 818-823, 1999) discloses that the soluble 18 KDa CD40L of the claimed invention cannot inhibit secondary IgG production from memory B cells (see Results, particularly pages 820-821 and Figure 3). Although Lazarus et al. discloses that soluble 18 KDa CD40L could prevent an increase in cell proliferation under certain conditions in a mixed-lymphocyte culture, this 18 KDa CD40L could not inhibit a MLR (see page 821 and Figure 4). Therefore, it appears that the soluble 18 KDa CD40L of the claimed invention may be able to inhibit certain immune responses associated with T cell function and alloimmune responses, soluble 18 KDa CD40L appears limited in the conditions of inhibiting alloimmune responses or T cell immune responses. Also, the Discussion acknowledges that the mechanisms of action by the ability of soluble 18KDa CD40L to inhibit a secondary alloimmune in a SCID mouse engrafted with human lymphocytes is unclear.

Nannizzi-Alaimo et al. (Circulation 105: 2849-2854, 2002) reports that soluble CD40L is a prothrombotic and proinflammatory protein which can contribute to thrombotic and inflammatory complications (See entire document, including Abstract).

In addition, the claims encompass preventing the diseases selected from the group set forth in claim 30. There is insufficient objective evidence that the claimed soluble 18 KDa CD40L can prevent such diseases, including diabetes, arthritis and SLE as set forth in claim 30. For example, the claimed targeted diseases and conditions set forth in claim 30 are treated after the diagnosis of such conditions and diseases.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies of inhibiting alloimmune or T cell responses with a known CD40L agonist, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating or preventing alloimmune or T cell mediated immune responses with the agonistic soluble 18 KDa CD40L employed in the claimed invention.

Applicant's arguments are not found persuasive.

5. Upon reconsideration of applicant's amended claims, the previous rejections under 35 U.S.C. § 102(e) as being anticipated by Armitage et al. (U.S. Patent No. 6,264,951) and Aruffo et al. (U.S. Patent No. 6,376,459 ) have been withdrawn.

6. No claim is allowed.

Again, applicant is invited to consider amending the claims to recite limitations that read on platelet alloimmunization.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
March 16, 2004